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In the Application of:

Kreutzer *et al.*

Serial No.: 09/889,802

Int'l Filing Date: January 29, 2000

For: Method and Medicament for Inhibiting the Expression of a Defined Gene

Examiner: Karen Lacourciere

Group Art Unit: 1635

Confirmation No.: 8835

APPROVED
SPRE, TC 1600

PROTEST UNDER 37 CFR 1.291(a)

Assistant Commissioner for Patents
Washington, D.C. 20231,

ATTENTION: John Doll
Director
Technology Center 1600

Introduction

The protestor requests that the arguments presented in this protest be considered during examination of this application. This application has not published, nor has a notice of allowance been issued.

This is a second protest filed by the protestor. The issues raised herein could not have been raised in the protestor's first protest because the file history was not publicly available at the time the first protest was filed and, therefore, the protestor did not and could not have known that the applicants had amended their claims and specification to encompass subject matter not supported in the original, publicly available disclosure. Specifically, the applicants have amended the claims and the specification to encompass genera of double stranded RNA (dsRNA) generally comprising a 3'-overhang and specifically comprising a single nucleotide 3'-overhang. As there is no written description support for such genera one could not have known that claims to such genera were or would be pursued until the file history became publicly available. In addition, the applicants have added claims directed to modified dsRNA species and specifically directed to modified dsRNA species comprising a 3' overhang. The specification contains no written

description support for modified dsRNAs comprising 3' overhangs. For all these reasons, this protest is proper.

As just suggested and explained more fully below, the undersigned, a third party to this patent application, protests any allowance of claims comprising double stranded RNA ("dsRNA"), modified or unmodified, with a 3'-overhang of any kind as there is no written description support in the specification for such constructs.

The Patent Office should have no misapprehension about the applicants' intent, which is to obtain broad claims to small interfering RNAs (siRNAs) important to the RNAi field. The disclosure of this application, however, came well before the seminal work of Tuschl, Zamore, and others, who those skilled in the field recognize as first discovering that dsRNA of 21-23 base pairs with 3' nucleotide overhangs is the active nucleic acid involved in RNAi. What the applicants have done is to take the knowledge learned subsequent to their filing and scour their own application for any scintilla of evidence that might support a claim to the commercially-important subject matter discovered by others subsequent to the filing of the present application. As evidenced by the claims the applicants are now pursing, it appears the applicants believe they have found such evidence. But as described below, the evidence is woefully insufficient to manifest possession at the time the present application was filed of the broad scope of what is now being claimed, and, therefore, such claims are unpatentable under 35 U.S.C. § 112, first paragraph.

None of the pending claims are adequately described in the specification as filed.

The first appearance of claims reciting dsRNA with a 3'-overhand was in a Fourth Preliminary Amendment filed March 11, 2003, nearly a year and a half after the filing date of the instant application (and more than three years from their earliest priority date). Accordingly, such claims do not enjoy the presumption of having written description support that originally-filed claims do. Manual of Patent Examining Procedure (MPEP) § 2163 *et seq.* (8th Ed., Rev. 2, May 2004).

The first appearance of any express reference to 3'-overhangs in the specification occurred by way of an amendment filed April 20, 2003, in which the applicants attempted to add the following language to the specification:

> The invention relates to an oligoribonucleotide having a double stranded structure (dsRNA). The oligonucleotide comprises two separate strands, wherein one strand of the

> dsRNA has a region which is complementary to an RNA transcript of at least a part of a target gene, wherein the region is not more than 49 nucleotides in length, and wherein the target gene is a mammalian gene. The oligoribonucleotide may have a length of between 15 and 49 base pairs, and the RNA transcript may be a primary or processed RNA. The oligoribonucleotide may comprise a linker between two RNA strands, such as a polyethylene glycol linker. The oligonucleotide may be modified so as to be resistant to RNA degradation. The oligoribonucleotide may comprise a 3' overhang, such as a single nucleotide overhang. The oligoribonucleotide may be 21 or 23 nucleotides in length.

This is also the first appearance of language reciting dsRNA of length 21 or 23 nucleotides. The reference to 23 nucleotides in the foregoing was subsequently deleted by the applicant.

It is telling that the applicants felt it necessary to add this **new** disclosure to the specification. The applicants' actions constitute nothing short of an admission that they realized that this disclosure was lacking in the specification as originally filed.

In their Fourth Preliminary Amendment the applicants presented a **four page** discussion (three pages and an appendix) of how the specification supports claims comprising dsRNA with 3'-overhangs. Again, it is telling that there was no express disclosure of 3'-overhangs on which the applicants could rely and that they had to go to some length in an attempt to extract from the specification what little was there.

The applicants' discussion of the alleged support for 3'-overhangs is based on "Use example 1" in the specification. Only through a painstakingly careful hindsight analysis were the applicants able to reason that the dsRNA generated in this example had a single nucleotide 3'-overhang at each end. We intentionally use the word "hindsight" because there is no mention in the specification that the dsRNA produced had a 3'-overhang, nor, accordingly, that there was any significance to it. Furthermore, the applicants neglected to mention in their explanation that **the dsRNA is over 300 base pairs long**!

The protestor respectfully submits that this single disclosure of a single dsRNA >300 base pairs in length that happened to inherently have a single nucleotide 3'-overhang is far from sufficient to support the breadth of claims now being pursued.[1] Moreover, the specification itself fails to discuss or even recognize this inherent structural feature or to convey to one of ordinary skill in the art any significance of it. There is nothing in the specification that would convey to one of

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[1] The pending claims are attached hereto as appendix A for the Examiner's convenience.

ordinary skill in the art that this structural feature was part of the invention or was intended to be employed with the dsRNA constructs of the invention.

In their other Example, "Use example 2," a 21-basepair dsRNA is described wherein the 3' ends are covalently linked using a chemical (C18) linker molecule. The applicants explain in their arguments in support of their amendments to the specification above that this short dsRNA also contains a 3'-nucleotide overhang. But that is not evident from the application as filed. This additional nucleotide is absent in the sequence listing (SEQ ID NO 8) submitted in the specification as filed.

Thus, the applicants' specification contains only a single example of a dsRNA having a 3'-nucleotide overhang, and this overhang comprises but a single nucleotide on a dsRNA molecule > 300 bp in length. We contend that this sparse teaching is completely inadequate for what is being now claimed, particularly with regard to short dsRNA species comprising 21 base pairs and in view of the complete lack of any teachings even acknowledging the existence of 3' overhangs, let alone placing any significance on them. At best the applicants' specification adequately describes a >300bp dsRNA species having a single nucleotide 3'-overhang.

Where species examples are relied upon for support for a genus the law is quite clear that the number of examples must be representative of the scope of the claim being sought. We submit that this single, inherent disclosure, unsupported by **any** additional teachings (express or inherent) suggesting 3'-overhangs were considered a structural feature of the inventive dsRNA would not convey to one of ordinary skill in the art that the applicants had possession of the broad range of dsRNA now being claimed. This is particularly true for dsRNAs 15-49 bps, which are not explicitly disclosed with or without 3'-overhangs with the exception of a single example that also comprises a covalently-attached organic linker molecule required for the resulting dsRNA to have biological activity.

In view of the foregoing, therefore, the protestor respectfully submits that the specification as filed contains insufficient written description support for any claim broadly directed to a dsRNA with a 3'-overhangs of any length other than the single, specific dsRNA of >300 base pairs described in example 1.

The specification also fails to support narrower embodiments, such as recited in new claim 242, which further limits claims 241 and 221 to 21 base pair dsRNAs with a single 3'-overhang nucleotide. This new claim, as all others discussed herein, cannot enjoy the presumption that the specification as filed provided an adequate written description, and the burden falls to the applicants to establish that their specification contains sufficient support for new claim 242. As detailed herein the applicants cannot sustain their burden.

The specification recites but one example of a dsRNA comprising 21 base pairs (in Example 2):

5'-ucgagcuggacggcgacguaa-C18-uuacgucgccguccagcucga-3'.

Significantly, this embodiment comprises a chemical linker connecting the two RNA strands and **does not comprise a 3'-overhang nucleotide** (the nucleotides of the two RNA strands exactly correspond in the Watson-Crick sense). Thus, not even the single example of a 21-mer dsRNA falls within the scope of new claim 242.

Neither does the remainder of the specification provide support for new claim 242. The specification recites dsRNA molecules having "not more than 49" and "15 - 49" base pairs (bp), albeit generically. What the specification actually discloses, however, are only certain species. And as we just discussed, these lone examples do not even fall within the recited scope of claim 242 - Example 1 describes a molecule having a single 3'-overhang nucleotide, but it is > 300 base pairs in length, and Example 2 recites a particular 21 base pair species of dsRNA but does not have a 3'-overhang nucleotide. It is evident that the disclosure of Examples 1 and 2 cannot provide written description support for the 21 base pair dsRNA with a single 3'-overhang nucleotide now claimed by applicants in claim 242.

Additionally, claim 242 encompasses 21 base pair dsRNA having a single 3'-overhang nucleotide regardless of whether the two RNA strands are chemically linked. But as described above, the single dsRNA molecule comprising 21 base pairs disclosed in the '802 specification as filed contains a C18 linker. This linker is an important component and is taught to be necessary for the dsRNA disclosed in Example 2 to be operative. Indeed, the applicants specifically state that "[t]he right fields of each of figures 4a and 4b show that YFP expression was not visibly inhibited when the single-stranded RNA was injected into the nuclei." (Page 19, lines 5-7.) The specific disclosure in Example 2 of a single 21-basepair dsRNA species with a chemical linker but without a 3'-overhang is inadequate to support a claim, like claim 242, that

encompasses 21-basepair dsRNAs having a single 3'-overhang nucleotide and no linker. Moreover, the application explicitly recites that the organic linker is a *necessary* feature of the smaller dsRNA molecules, stating "[t]his result demonstrates that even shorter dsRNAs can be used for specifically inhibiting gene expression in mammals *when the double strands are stabilized by chemically linking the single strands*." P. 19, ll. 15-18 (*emphasis* added). Thus, the teaching of Example 2 is limited to this particular 21 bp fragment wherein the strands are perfectly matched in the Watson-Crick sense and covalently linked using an organic linker, and does not provide written description support generally for all 21-basepair dsRNA species having a single 3'-overhang nucleotide lacking a covalently-bound chemical linker at the 3' end. The specification only teaches short (21-bp) dsRNA without a 3'-overhang nucleotide and requiring a chemical linker to be active.

The specification as filed does not contain a written description of modified dsRNAs

Claims 239 and 245 were added in the applicants' Fourth Preliminary Amendment filed March 7, 2003. Thus, these claims are not entitled to any presumption that the specification as filed provides adequate support for these claims. Manual of Patent Examining Procedure (MPEP) § 2163 et seq. (8th Ed., Rev. 2, May 2004). Indeed, as set forth in detail herein, the specification of the '802 application is neither entitled to the presumption nor in fact supports these claims with an adequate written description as required by 35 U.S.C. §112, 1st paragraph. The scope of the disclosure does not disclose the invention with sufficient particularity to indicate to one of ordinary skill in the art that the inventors were in possession of the invention throughout its broadest scope.

These claims are directed to dsRNAs modified to be resistant to degradation (see Appendix A for the text of these claims). However, the specification contains but sparse support for any dsRNA modifications, as evidenced by the paucity of disclosure even the applicants themselves were able to find after no doubt extensive and thorough review of their specification.

The applicants cite but four portions of the specification in support of these new claims. The first citation, at page 12, lines 22-30, is merely a discussion of methods for removing ssRNA contaminants *from a dsRNA preparation*. There is no teaching in this portion of the specification that the dsRNA strands should be modified to render them resistant to the plurality of

ribonucleases taught by the specification to be useful in removing ssRNA contaminants of the dsRNA preparation.

The second citation, at page 4, line 37-38 is at least explicitly directed to modifications. However, the teachings are limited to modification of the 5'- or 3'-ends of the dsRNA. This teaching is woefully inadequate to support the two broad claims to dsRNA modified at any position (other than by covalent attachment of a chemical linker at the 3' end) within the dsRNA to be resistant to any kind of degradation (exonucleolytic, endonucleolytic, chemical, physical, enzymatic or otherwise).

In citation number 3, at page 5, lines 7-10, the applicants return to their practice of citing a portion of the specification that has no bearing on the dsRNA modification claims. This portion of the specification teaches incorporation of a linker between the two complementary RNA strands. This is a particular, specific, and idiosyncratic use of the term "dsRNA modification" which would not be understood in the art to support the broad range of modifications encompassed by claims 239 and 245. Moreover, there is no teaching that incorporation of this linker would be related in any way to resistance to RNA degradation. Indeed, the function of the linker is to promote hybridization of the two ssRNA molecules to a dsRNA molecule, wherein the dsRNA is resistant to ssRNA-specific nucleases. At best, the linker may be considered to be a modification that increases resistance to exonucleolytic degradation by occupying two of the four ends of the dsRNA molecule. Again, we contend that one of ordinary skill would not have interpreted hybridization to produce dsRNA from ssRNA to constitute "modified RNA."

Finally, the applicants cite page 5, lines 15-18 that discloses that chemical modification of ribonucleotides in "the loop region" between the two strands of a dsRNA promotes resistance to degradation. This disclosure is thus specifically limited to ssRNA (*i.e.*, **single** stranded RNA) in a hairpin structure where the dsRNA is formed having ssRNA in the hairpin.

None of these citations, specifically selected by the applicants in support of their pending claims supports these broad claims to any oligoribonucleotide, have any nucleotide modification in any dsRNA to make the oligoribonucleotide resistant to degradation. Because these claims are newly-added claims, the burden falls on the applicants to make a showing that these claims are supported by the specification as files. That they cannot is fully evidenced by their own citations to their own, deficient specification. Since the applicants cannot sustain their burden to establish

sufficient support of these claims, the claims are unpatentable for failure to satisfy the written description requirement of 35 U.S.C. §112, first paragraph.

Service on Applicant

A copy of this document is being served on Kathleen Williams, attorney of record for the applicants.

Date: 11/23/04 By: _____

Eric Schellin

Appendix A

Serial No.: 09/889,802

The following Listing of the Claims will replace all prior versions and all prior listings of the claims in the present application:

Listing of The Claims:

1-220. (Canceled)

221. (Currently Amended) An isolated oligoribonucleotide consisting of ~~comprising~~ two separate RNA strands, a self-complementary double stranded structure, (dsRNA), and a 3' overhang, said double stranded structure being complementary to less than the full length of an RNA transcript of a mammalian target gene, and not comprising a full length RNA transcript of said mammalian target gene, wherein the structure is not more than 49 nucleotides in length, and wherein the oligoribonucleotide specifically inhibits the expression of said target gene.

222. (Previously presented) The oligoribonucleotide of claim 221, wherein said oligoribonucleotide consists of a length of between 15 and 49 nucleotides.

223. (Previously presented) The oligoribonucleotide of claim 221 and 224, wherein the RNA transcript is a primary or a processed RNA.

224. (Currently Amended) An isolated oligoribonucleotide~~, having~~ consisting of a self-complementary double stranded structure (dsRNA) consisting of two ~~self-complementary~~ RNA strands of not more than 49 nucleotides in length, wherein the dsRNA comprises a linker between the two RNA strands, wherein said structure is fully complementary to an RNA transcript of a mammalian target gene, wherein the dsRNA comprises a 3' overhang, and wherein the oligoribonucleotide specifically inhibits the expression of said target gene.

225. (Previously presented) The oligoribonucleotide of claim 224, wherein the linker is a polyethylene glycol linker.

226-231. (Canceled).

232. (Currently Amended) An isolated mammalian cell comprising an exogenous oligoribonucleotide, wherein the oligoribonucleotide ~~has~~ consists of a self-complementary double stranded structure (dsRNA) ~~comprising~~ consisting of two separate RNA strands, wherein the dsRNA comprises a 3' overhang, wherein one strand of the dsRNA has a region which is complementary to an RNA transcript of a target gene, and wherein the dsRNA specifically inhibits the expression of said target gene.

233. (Previously Presented) The mammalian cell of claim 232, wherein the mammalian cell is a human cell.

234. (Previously Presented) The mammalian cell of claim 232, wherein the region is not more than 49 nucleotides in length.

235. (Previously Presented) The mammalian cell of claim 232, wherein the dsRNA has a length of between 15 and 49 base pairs.

236. (Previously Presented) The mammalian cell of claim 232 and 237, wherein the RNA transcript is a primary or a processed RNA.

237. (Currently Amended) An isolated mammalian cell comprising an exogenous oligoribonucleotide, wherein the oligoribonucleotide ~~has~~ consists of a self-complementary double stranded structure (dsRNA) ~~comprising~~ consisting of two RNA strands, wherein the dsRNA comprises a 3' overhang and is fully complementary to an RNA transcript of a target gene, wherein the dsRNA comprises a linker between the two RNA strands, and wherein the dsRNA specifically inhibits the expression of said target gene.

238. (Previously Presented) The mammalian cell of claim 237, wherein the linker is a polyethylene glycol linker.

239. (Previously Presented) The oligoribonucleotide of claim 221, wherein said dsRNA is modified so as to be resistant to RNA degradation.

240. (Canceled).

241. (Previously Presented) The oligoribonucleotide of claim 221, wherein said 3' overhang is a single nucleotide overhang.

242. (Previously Presented) The oligoribonucleotide of claim 241, wherein said oligoribonucleotide is 21 nucleotides in length.

243. (Previously Presented) A composition comprising an oligoribonucleotide according to claim 221 and 224.

244. (Previously Presented) The composition of claim 243, further comprising a second oligoribonucleotide, wherein said second oligoribonucleotide differs in sequence from said oligoribonucleotide.

245. (Previously Presented) The mammalian cell of claim 232 and 237, wherein said dsRNA is modified so as to be resistant to RNA degradation.

246. (Canceled).

247. (Previously Presented) The mammalian cell of claim 232 and 237, wherein said 3' overhang is a single nucleotide overhang.

248. (Previously Presented) The mammalian cell of claim 232, wherein said exogenous oligoribonucleotide is vector encoded.

249. (Currently Amended) The oligoribonucleotide of Claim 221, wherein said double-stranded ~~region~~ structure is fully complementary to less than the full length of an RNA transcript of a mammalian target gene.

250. (Previously Presented) A vector encoding the oligoribonucleotide of claim 221 or 224.

251. (Previously Presented) The oligoribonucleotide of claim 224, wherein said double stranded structure consists of two self-complementary RNA strands of 15 to 49 nucleotides.

252. (New) An isolated oligoribonucleotide consisting of two separate RNA strands, a double stranded structure, (dsRNA), and a 3' overhang, said double stranded structure being fully complementary to less than the full length of an RNA transcript of a mammalian target gene, and not comprising a full length RNA transcript of said mammalian target gene, wherein the structure is not more than 49 nucleotides in length, and wherein the oligoribonucleotide specifically inhibits the expression of said target gene.

253. (New) The isolated mammalian cell of claim 232, wherein said one strand of the dsRNA is fully complementary to an RNA transcript of a target gene.

254. (New) An isolated mammalian cell comprising an exogenous oligoribonucleotide, wherein the oligoribonucleotide consists of a double stranded structure (dsRNA) consisting of two separate RNA strands, wherein the dsRNA comprises a 3' overhang, wherein one strand of the dsRNA is fully complementary to an RNA transcript of a target gene, and wherein the dsRNA specifically inhibits the expression of said target gene.